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Multiple Endocrinopathies in an Infant With Fatal Neurodegenerative Disease

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We report on a male infant with congenital hypoparathyroidism who developed primary hypothyroidism at 3 months and insulin-dependent diabetes mellitus at 25 months. He had evidence of widespread and progressive neurologic dysfunction characterized by severe developmental delay, blindness, deafness, seizures, atrophy of the cerebellar and frontal lobes, and elevated spinal fluid protein. Also noted were renal hypoplasia, hyporeninemic hypoaldosteronism, chronic anemia, persistent elevation of liver transaminase levels, abnormal intraventricular cardiac conduction, reduction in numbers of helper T-cells, and distinctive facial anomalies. The child died of multiorgan failure at 29 months. A mitochondrial basis for the syndrome was considered but a molecular mechanism has, as yet, not been identified. Am. J. Med. Genet. 69:271–279, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: hypoparathyroidism; diabetes mellitus; renal insufficiency; growth failure; neurodegeneration; mitochondrial

INTRODUCTION

Multiple endocrine failure in infancy is rare. In older children, it is usually the result of autoimmune-mediated glandular destruction. In infancy, autoimmune endocrine disease usually involves the pancreatic islets and results in diabetes mellitus [Neufeld et al., 1980; Arslanian et al., 1985; Vardi et al., 1988]. However, autoimmune destruction of multiple endocrine glands, resulting in polyendocrinopathy, has not been reported in infants. We describe an infant with non-autoimmune failure of the parathyroids, thyroid gland, and pancreatic islets. Additionally, he had progressive neurodegenerative disease, chronic anemia, renal insufficiency, and growth failure. He died at 29 months of multiorgan failure. We think that he has a previously undescribed syndrome. Although the cause of his disease was not established, we suspect a disorder of energy production, perhaps mitochondrial in origin.

Patient Description

The salient manifestations are summarized in Table I. MP was born at term to non-consanguineous Caucasian parents. The pregnancy and delivery were uncomplicated. His birth weight was 2.75 kg; birth length was 48.3 cms. His facial appearance was normal at birth and during the first several months of life (Fig. 1A). However, after 4–6 months (Fig. 1B) he developed a round face, prominent forehead, carp-shaped mouth with thin lips, enophthalmia, microphthalmia, and dystichiasis. He had narrow nasolacrimal ducts resulting in continuous epiphora. The scalp hair was fine, brittle, and remained scant throughout life.

The infant was well until age 9 days when generalized seizures occurred. A diagnosis of primary hypoparathyroidism was made based on the presence of hypocalcemia, hyperphosphatemia, a normal serum magnesium level, and a low parathormone value as detailed in Table II; renal function was normal. Treatment with calcitriol and calcium gluconate was initiated. The clinical course strongly suggested that the hypoparathyroidism was permanent. First, frequent adjustments of the doses of calcitriol and calcium gluconate were needed over the first 8 months because of recurrent hypocalcemic seizures. Second, hypocalcemic seizures recurred at age 20 months when he was placed on a potassium-binding resin to treat hyperkalemia (potassium 6.1 mEq/L); the calcium levels stabilized after discontinuing the resin. Finally, at age 24 months, his serum calcium and phosphorus levels were 5.5 mg/dl and 9.6 mg/dl, respectively, during an episode of gastroenteritis, when calcitriol therapy was omitted.

Further testing was undertaken to establish the

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TABLE I. Summary of Clinical Manifestations and Progression Noted in MP

Age (months)	Clinical findings
Birth	Hypoparathyroidism
1–3	Primary hypothyroidism, mild renal insufficiency, elevated transaminases
4–7	Onset of facial anomalies, growth failure, microcephaly, progressive psychomotor retardation, deafness, hypotonia, retinal degeneration, blindness, hypochromic normocytic anemia
19–24	Small kidneys, hyporeninemic hypoaldosteronism, bilateral ptosis, variable esotropia
25–27	Insulinopenic diabetes mellitus, intraventricular cardiac conduction defect, progressive encephalopathy with seizures, abnormal EEG, increasing spinal fluid protein
29	Progressive renal failure, anasarca, fulminant sepsis, death

cause of the hypoparathyroidism. DiGeorge syndrome was excluded on the basis of a normal thymic shadow on a chest radiograph, absence of anatomic abnormalities of the great vessels of the heart, and lack of the characteristic deletion on the long arm of chromosome 22 observed in most patients with DiGeorge syndrome [de la Chapelle et al., 1981; Greenberg et al., 1986; Kelley et al., 1982]. In addition, the persistent decrease in CD2, CD3, and CD4 T-lymphocytes, as well as the normal numbers of CD8 cells and decreased levels of IgG2, were not typical of DiGeorge syndrome (Table III). Apart from episodic watery diarrhea and an episode of severe bronchiolitis related to an infection with respiratory syncytial virus, MP had no clinical evidence of immune deficiency.

In addition to neonatal hypoparathyroidism, MP also developed other endocrinopathies. Compensated primary hypothyroidism was evident at 3 months of age (Table III); anti-thyroid antibodies (anti-thyroglobulin, and anti-thyroid peroxidase antibodies) were absent, indicating that an autoimmune cause was unlikely. He remained clinically and biochemically euthyroid on standard replacement doses of L-thyroxine. At age 25 months, hyperglycemia and relative insulinopenia were detected (Table III). Islet cell and insulin autoantibodies were not present. Good glycemic control was achieved with twice daily insulin injections (0.4–0.6 U/kg/d); the hemoglobin A1c on this regimen was 6.7% (normal: 4.5 ± 0.3; mean ± SD). Neither ketonuria nor acidosis ever occurred. At 26 mo, insulin therapy was withdrawn for 36 hours following a hypoglycemic seizure. Hyperglycemia recurred, thus confirming the diagnosis of diabetes mellitus.

Linear growth, although poor from birth to 18 months, inexplicably improved somewhat thereafter (Fig. 2). The skeletal age was significantly retarded; at 25 months, the bone age was 3 months. Dental eruption was similarly delayed with only 6 teeth at 29 months. Interpretation of the results of provocative growth hormone testing and levels of IGF binding proteins was confounded by the concomitant malnourished and insulinopenic states [Clemmons et al., 1989; Salardi et al., 1986; Shisko et al., 1994; Soliman et al., 1986]. Weight gain improved markedly after the institution of insulin therapy.

MP had severe neurodevelopmental abnormalities including profound hypotonia, deafness, and psychomotor retardation evident from age 3 to 4 months. The only developmental progress made by 29 months of age was an inconsistent social smile. He had generalized areflexia. Microcephaly was first noted at age 5 months, and the head circumference was 42.6 cm (–7 SD) at death (Fig. 2B). A magnetic resonance imaging (MRI) study of the brain at the age of 7 months demonstrated atrophy of the frontal lobes and cerebellum. An electromyogram (EMG) was normal. Multiple brainstem auditory evoked response studies were consistent with bilateral sensorineural deafness. Initially,

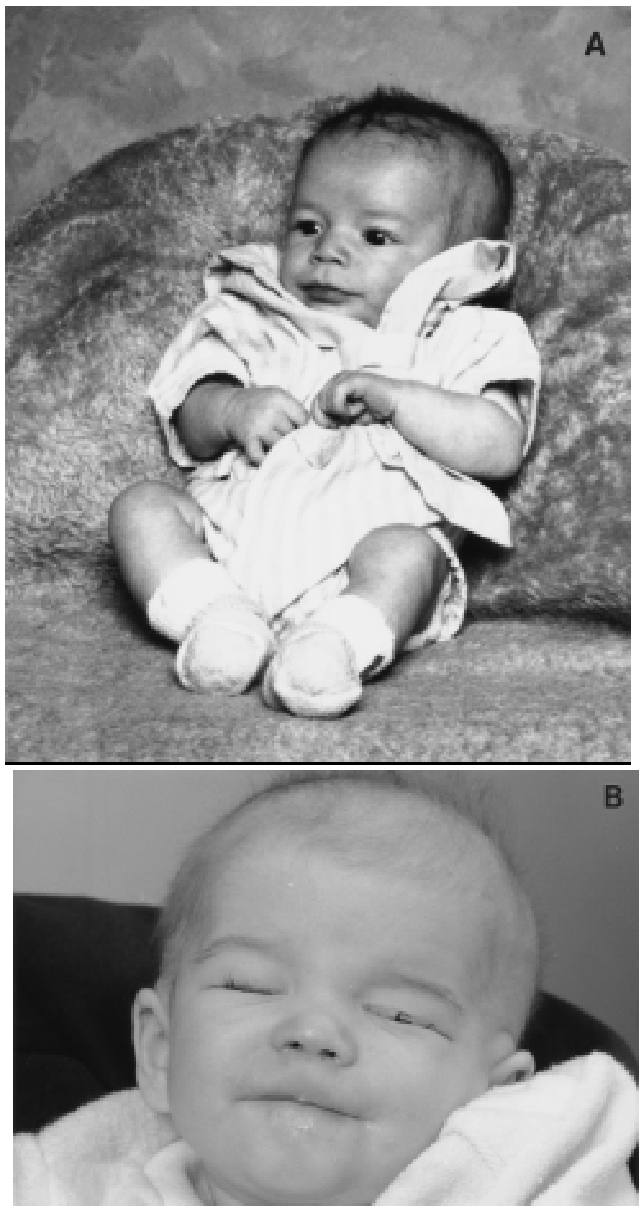

Fig. 1. Facial features. **A:** Relatively normal features at 2 months of age apart from prominent forehead. **B:** Facial features at 26 months of age.

TABLE II. Results of Some Laboratory Studies in the Patient Described

Lab test[a]	Results									
	9 days	3 mos	7 mos	8 mos	12 mos	20 mos	25 mos	27 mos	28 mos	29 mos
Calcium (8.4–10.6 mg/dl)	5.1	9.3	8.1	7.0	10.8	—	9.2	8.9	7.5	9.0
Phosphorus (2.5–4.5 mg/dl)	13.2	6.6	6.3	4.2	5.2	—	2.3	—	4.8	5.8
Magnesium (1.6–2.9 mg/dl)	2.0	—	—	—	—	—	—	—	—	1.6
PTH (10–65 pg/ml)	1.0	—	—	—	—	—	—	—	—	—
Thyroxine (5–12 μg/dl)	—	9.5	5.3	5.5	10.9	—	11.0	9.2	—	—
Thyrotropin (0.2–6.2 μIU/ml)	—	8.01	29.9[d]	14.3	7.97	—	5.0	5.74	—	—
Anti-thyroid antibodies (<1.0 U/ml)	—	—	<0.3	—	—	—	—	—	—	—
C-peptide (0.9–4.2 ng/ml)[b]	—	—	—	—	—	—	1.14	—	—	—
Glucose (65–110 mg/dl)[b]	64	98	65	51	106	—	635–1,036[e]	250	190	31
Sodium (135–145 mmol/L)	141	135	140	136	139	129	129	132	138	139
Potassium (3.5–5.5 mmol/L)	4.8	5.2	4.7	5.1	4.8	6.1	5.6	6.1	4.2	3.9
Bicarbonate (20–25 mmol/L)	19	17	24	21	21	—	21	27	21	27
BUN (5–25 mg/dl)	9	20	31	4	54	—	35	30	37	39
Creatinine (0.2–0.4 mg/dl)	0.9	0.4	0.7	0.8	0.7	—	0.8	0.7	0.8	1.3
SGOT (10–54 IU/L)	—	180	104	—	135	—	77	60	270	269
Random cortisol (6–18 μg/dl)	—	—	—	—	—	—	44.2	—	—	9.8
Aldosterone (8–100 ng/dl)	—	—	—	—	—	—	—	5.3[c]	—	—
Renin (>5 ng/ml/90min)	—	—	—	—	—	—	—	3.49	—	—
Hemoglobin (10.5–13.5 gm/dl)	16.8	10.4	6.5	6.9	10.7	—	6.9	8.0	7.2	7.9

[a]Normal values in parentheses.
[b]Normal fasting levels.
[c]Following sodium restriction (<1 meq/kg/day) for 36 hours; normal levels correspond to unrestricted NaCl intake.
[d]Treatment with synthroid started.
[e]Insulin therapy initiated.

MP appeared to see, and visual evoked responses were normal at 4 months of age. At age 7 months, examination of his eyes under anesthesia revealed paucity of retinal vascular arcades, optic atrophy, diffuse pigmentary retinopathy, and macular gliosis. An electroretinogram (ERG) was flat. The retinal degenerative process was progressive. At age 19 months, bilateral ptosis and variable esotropia were noted. Despite these findings, his overall neurologic status was relatively static until age 26 months after which he developed a progressive encephalopathy. He had multiple seizures which were not associated with hypocalcemia or hypoglycemia and required anticonvulsant therapy. Electroencephalogram (EEG) recordings showed progressive slowing of background activity. Serial lumbar puncture studies demonstrated progressive increase in the level of spinal fluid protein (23 mg/dl at age 25 months, 81 mg/dl at 27 months, 93 mg/dl at 28 months, and 136 mg/dl pre-terminally).

MP also had chronic renal insufficiency which was clinically insignificant until the last month of life. Elevated levels of creatinine and BUN were evident from age 1 month (Table II). At age 5 months, a computerized tomogram (CT) scan of the abdomen showed mild rotational abnormalities of both kidneys, which were otherwise normal. Initially, serial sonographic evaluations showed kidney size at the lower end of the normal range for age. At 19 months, both kidneys were small for age and weight, and had not grown over the previous 6 months. A technetium-99 diethelenetriamine pentacetate (DTPA) scan documented decreased renal function. On cystoscopy, a web in the mid bulbous ure-

TABLE III. Results of Immunology Studies in the Patient Described

Age (months)	5	9	12	21	29[b]
Total WBC/mm^3	8,400	—	8,500	7,900	5,800
T cell subsets					
Total lymphocytes/mm^3	648 (5,395–7,211)	—	2,221 (5,284–6,714)	3,239 (4431–5,508)	4,505 (3,855–5,248)
CD2/mm^3	303 (3,929–5,275)	—	1,465 (3,806–4,881)	2,124 (3,101–3,868)	1,717 (2,649–3,639)
CD3/mm^3	246 (3,505–5,009)	—	1,333 (3,409–4,575)	1,926 (2,766–3,508)	1,975 (2,324–3,295)
CD4/mm^3	195 (2,780–3,909)	—	310 (2,630–3,499)	441 (1,919–2,472)	1,023 (1,538–2,213)
CD8/mm^3	127 (351–2,479)	—	666 (351–2,479)	969 (351–2,479)	1,378 (351–2,479)
CD4:CD8	1.5 (1.2–6.2)	—	0.46 (1.2–6.2)	0.45 (1.2–6.2)	0.74 (1.2–6.2)
Immunoglobulins[a]					
IgA	—	34 (14–106)	22 (17–123)	72 (17–123)	—
IgG total	—	327 (442–880)	395 (553–971)	1,110 (553–971)	—
IgG_1	—	225 (286–680)	290 (286–680)	1,040 (286–680)	—
IgG_2	—	2 (30–327)	20 (30–327)	5 (30–327)	—
IgG_3	—	30 (13–82)	60 (13–82)	90 (13–82)	—
IgG_4	—	4 (1–65)	3 (1–65)	10 (1–65)	—
IgM	—	91 (34–149)	77 (43–173)	95 (43–173)	—

[a]Normal values for age in parentheses in mg/dl.
[b]Normal values for age in parentheses while receiving 100 mg/m^2/d hydrocortisone.

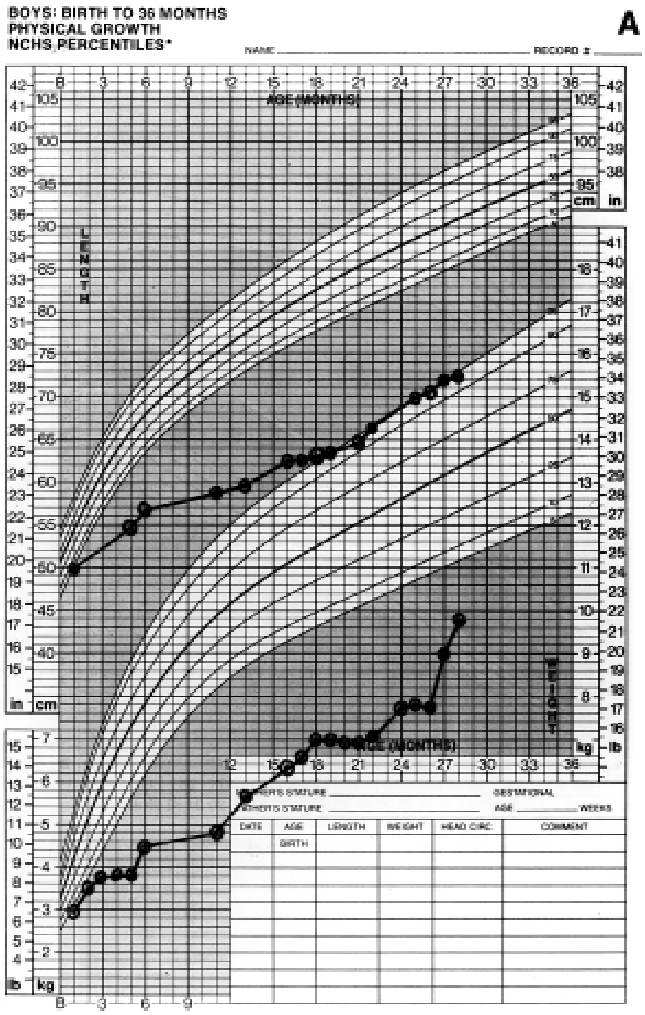

Fig. 2. **A:** Weight and linear growth. Treatment for primary hypothyroidism was initiated at 7 months of age; insulin was started at 25 months. **B:** Head circumference.

thra was noted and excised with no improvement in renal function.

Although MP had renal insufficiency, his serum electrolytes remained normal until age 20 months when he developed hyperkalemia and hyponatremia without metabolic acidosis (Table II). Addison disease was excluded by a normal metyrapone test, as well as random cortisol levels as high as 44.2 μg/dl. In view of the renal abnormality, hyporeninemic hypoaldosteronism was suspected and confirmed by a sodium deprivation test at 27 months of age. Serum sodium and potassium levels normalized on mineralocorticoid supplementation with 0.1 mg fluodrocortisone.

In addition to endocrine, neuromuscular, and renal dysfunction, MP also had chronically elevated transaminase levels, chronic anemia and evidence of a cardiac conduction defect. Hypochromic, normocytic anemia, not responsive to iron, was noted from age 5 months and required frequent transfusions. An elevated level of erythropoetin of 69.3 mU/ml was measured when the hemoglobin level was 8.0 mg/dl. An electrocardiogram (ECG) examination at 26 months demonstrated a mild right intraventricular conduction defect; however, arrhythmias were never observed.

Although MP had multiple medical problems, his clinical condition remained relatively stable until 27 months. Progressive encephalopathy, characterized by seizures and increasing spinal fluid protein concentration heralded a rapid deterioration. Intractable clinical and subclinical seizures occurred and were treated with high dose anticonvulsants and prolonged ventilatory support. Anasarca, associated with hypoalbuminemia, occurred and was complicated by acute renal insufficiency and fungal sepsis. Progressive acidosis supervened and vigorous resuscitation was withheld. Immediate postmortem biopsies of liver and quadriceps were obtained and frozen for subsequent DNA analysis.

Analysis of his chromosomes obtained from blood cells did not show any abnormality, in particular, no deletions of chromosomes 10 or 22 were apparent.

Autopsy

Gross. Gross anasarca was noted. *Enterobacter clocae* and *Candida tropicalis* were recovered from blood and body fluids. The liver was yellow, soft and enlarged. The kidneys were hypoplastic (right 21.5 g, left 30.5 g) with persistent fetal lobulation. The thyroid gland was hypoplastic with follicular atrophy and fibrosis. Parathyroid glands were not seen. The thymus and pancreas were hypoplastic. Autopsy findings in the central nervous system confirmed the antemortem radiographic findings. The optic nerves were small; the frontal lobes and cerebellum were significantly atrophic or underdeveloped.

Microscopic. Focal hyaline membranes were noted in the lungs together with dilated airways and mucous plugs. The pancreas was fibrotic with cystic dilatation of ducts filled with mucin; severe islet cell depletion was noted. Peyer patches were depleted in the gastrointestinal tract. The liver had areas of micro- and mac-

rovesicular steatosis. The testicular tubules were atrophic. Diffuse neuronal loss was detected, most marked in the calcarine cortex, hippocampus, and internal granular layer of the cerebellum and to a lesser extent in the cerebral cortices. Severe gliosis was found in the calcarine cortex, hippocampus, cerebellar cortex, and optic nerves. Electron microscopic examination of the liver, skeletal muscle, and cardiac muscle was unremarkable; ragged red fibers were absent.

Family

MP had no sibs. No other relatives had the phenotypic constellation of MP. A paternal great grandfather and maternal great grandmother had diabetes mellitus. Twenty-four hour urinary C-peptide levels in the non-diabetic parents and maternal grandmother were normal suggesting adequate rates of insulin secretion. No relatives had deafness, stroke, or visual, renal, or other endocrine problems.

METHODS AND RESULTS

The phenotypic expression in individuals with deletions and mutations in mitochondrial DNA is highly variable, but includes various combinations of diabetes mellitus [Gerbitz et al., 1993; Goto et al., 1991; Moares et al., 1989; Pilz et al., 1994], hypoparathyroidism [Zupanc et al., 1991], retinal degeneration [Howell et al., 1991; Huoponen et al., 1991; Johns and Smith et al., 1993; Johns and Heher et al., 1993], deafness [Gerbitz et al., 1993; Goto et al., 1991; Moares et al., 1989; Pilz et al., 1989], renal disease [Majander et al., 1991; Superti-Furga et al., 1993; Venkataraman et al., 1987; Zupanc et al., 1991], and mental retardation [Newman et al., 1991; Tatuch et al., 1992]. Accordingly, we isolated DNA and looked for deletions and mutations of the mitochondrial genome. Among the abnormalities we searched for were the recently described MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) mutations at nucleotide positions 3243 [Kishimoto et al., 1995] and 3271 [Goto et al., 1991] found in subjects with diabetes mellitus and nerve deafness. We also looked for the mutation at basepair position 8993 of the mitochondrial DNA which has been noted in individuals with neurogenic muscle weakness, ataxia and retinitis pigmentosa [Holt et al., 1990].

Skeletal Muscle

DNA was isolated from skeletal muscle. Southern blot analysis after digestion with endonucleases did not reveal any DNA deletions or re-arrangements. To detect the MELAS mutation, the oligonucleotide primers described by Kishimoto et al. were used [1990]. The fragment of mitochondrial DNA from base pair 3029 to 3610 was amplified with the polymerase chain reaction. The MELAS mutation is an A → G substitution at position 3243 of mitochondrial leucine tRNA which introduces a new restriction site when digested with the endonuclease, *Apa* I. In subjects with the MELAS mutation, digestion with *Apa* I results in two DNA fragments, 214 and 367 bp, on the agarose gel whereas normal subjects have only one band, 581 bp. Using this technique, the MELAS mutation at 3243 was not detected in MP (data not shown).

Peripheral Leukocytes

DNA was isolated from blood cells. Appropriate fragments encompassing the region of the known mutations were amplified by polymerase chain reaction (PCR) using α-32P d ATP to label the PCR products, and digested with diagnostic restriction enzymes. Digested DNA was electrophoresed through a 12% nondenaturing polyacrylamide gel, dried, and detected by autoradiography.

To detect the A → G mutation at nucleotide position 3243, we used oligonucleotide primers corresponding to positions nt 3116-3134 (forward) and nt 3353-3333 (backward) to amplify a 238 base pair fragment. The mutation creates an additional Hae III site such that a 169 base pair is converted into 2 fragments (97 and 72 base pairs, respectively). To detect the T → C mutation at nucleotide position 3271, we used oligonucleotide primers corresponding to positions nt 2164-2187 (forward) and nt 3295-3272 (backward). The backward primer contains a mismatch at position 3275, a G instead of a C. A T → C mutation at 3271 creates an additional Dde I cleavage site, such that a 103 base pair piece is cleaved into 2 fragments (79 and 24 base pairs, respectively). To detect the T → G or T → C mutation at nucleotide position 8993, we used oligonucleotide primers corresponding to positions nt 7955-7979 (forward) and 9950-9931 (backward) to amplify a 1995 base pair fragment. The mutations (T → G or T → C) create an additional Msp1 site such that a 1142 base pair fragment is cleaved into 2 fragments (842 and 300 base pairs, respectively).

Using these techniques, no mutation at 3243, 3271, or 8993 was found in leukocytes.

DISCUSSION

We have described an infant with an unrecognized syndrome of polyendocrine and growth failure, facial changes, severe developmental delay, seizures, blindness, deafness, chronic renal insufficiency, persistently elevated liver enzymes, anemia, and low levels of helper T-cells. Such widespread, multisystem pathology, and in particular, the involvement of multiple endocrine glands during infancy, makes our patient unique.

The first endocrinopathy noted in our patient was primary hypoparathyroidism. Although various causes of hypoparathyroidism, with onset in the neonatal period, have been described, our patient did not seem to have any of the recognized forms. Certainly, he did not have transient hypoparathyroidism which has been associated with prematurity [Tsang et al., 1973; Venkataraman et al., 1986], perinatal asphyxia [Aarskog and Harrison, 1994], and maternal diabetes [Noguchi et al., 1980; Venkataraman et al., 1987]. Permanent congenital hypoparathyroidism, as our patient had, is rare. It is most frequently seen as a component of DiGeorge syndrome, a triad of thymic hypoplasia, hypoparathyroidism, and cardiac anomalies associated with typical facial anomalies. Primary hypothyroidism and renal insufficiency have been reported in a few patients [Ger-

bitz et al., 1990; Gosseye et al., 1982; Muller et al., 1988]. Pericentromeric deletions of chromosome 22 have been found in most affected children [Dallapicola et al., 1989; de la Chapelle et al., 1981; Greenberg et al., 1988; Kelley et al., 1982; Matsuoko et al., 1994; Wilson et al., 1993]. However, for several reasons we do not think our patient had DiGeorge syndrome. First, the facial traits bore no resemblance to those classically described [Greenberg, 1993; Muller et al., 1988]. Second, the magnitude of the growth failure and severity of the mental retardation were uncharacteristic [Greenberg, 1993; Muller et al., 1988]. Third, the mild cardiac conduction defect noted in our patient, was not typical of the conotruncal and aortic arch abnormalities reported in DiGeorge syndrome [Muller et al., 1988]. Fourth, deafness, brain atrophy, retinal degeneration, liver dysfunction, hypoplastic anemia, and insulin-dependent diabetes mellitus are not part of this dysembryogenesis syndrome. Additionally, we detected no deletions of chromosome 22. Finally, the immunologic abnormalities which our patient had included persistent lymphopenia, low levels of helper T cells (CD4+), and diminished levels of IgG2. These contrast with the persistent depletion of suppressor T cells (CD8+) and low levels of IgA described in patients with DiGeorge syndrome [Buckley, 1987; Durandy et al., 1986; Muller et al., 1988; Reinherz et al., 1981].

Children with deletion of the short arm of chromosome 10 have many anomalies in common with DiGeorge syndrome including neonatal onset of hypoparathyroidism, anatomic cardiac defects, and T-cell abnormalities [Greenberg et al., 1986]. Although the T-cell abnormalities described in one patient with 10p- syndrome are similar to the defects seen in our patient, we did not detect any deletion of chromosome 10.

Our patient bears some resemblance to children recently identified with new forms of neonatal hypoparathyroidism associated with multisystem abnormalities. In 2 studies, a total of 20 children from the Middle East were reported with neonatal hypoparathyroidism of probable autosomal recessive inheritance [Richardson and Kirk, 1990; Sanjad et al., 1991]. In addition to hypoparathyroidism, these children had mental retardation, severe growth failure of intrauterine origin, and microcephaly, deep-set eyes, and thin lips; most had abnormalities in the shape and position of the ears, prominent forehead, microphthalmia, micrognathia, and depressed nasal bridge. None had hypothyroidism or diabetes mellitus. Four of these children had reduced numbers of T-cells; 7 had medullary stenosis of the long bones. Nine died during infancy or childhood, 7 of whom had recurrent infections.

Shaw et al. have described another autosomal recessive form of congenital hypoparathyroidism in 4 children from an Asian kindred [Shaw et al., 1991]. This phenotype also included renal tubular acidosis, progressive renal insufficiency, severe developmental delay, failure to thrive of postnatal onset, and sensorineural deafness. Two of the 4 had low numbers of T-cells; 1 had probable pancreatic exocrine insufficiency; 2 had hyperoxaluria. All died before 15 months of age. None had hypothyroidism, diabetes mellitus, or abnormal facial features.

Our patient had some manifestations in common with the Middle Eastern and Asian children reported in these 3 studies. However, multiple endocrine involvement, blindness, neurodegeneration with seizures, chronic anemia, and a cardiac conduction defect seem to make our patient unique. Furthermore, the absence of recurrent infections and skeletal abnormalities set our patient apart from the children with these newly reported syndromes.

MP is also different from the recently reported individuals with various combinations of asymptomatic hypoparathyroidism, sensorineural deafness, renal dysplasia, and diabetes mellitus [Bilous et al., 1992]. None of these patients came to medical attention during the neonatal period and none had T-cell abnormalities, minor anomalies, or hypothyroidism. The inheritance in this family was autosomal dominant, a mode of transmission which is not apparent in our patient's family. The patient reported here could have had his condition as an autosomal recessive or X-linked disorder, or could represent a new mutation.

Other forms of hypoparathyroidism have also been reported in infancy, including X-linked recessive [Penden, 1960], autosomal dominant [Arnold et al., 1990], and autosomal recessive [Parkinson and Thakker, 1992] varieties. In all of these, hypoparathyroidism is an isolated finding and, as such, were not diagnostic possibilities in our patient. Likewise, we discounted other causes of hypoparathyroidism, such as those seen in conjunction with Russell-Silver syndrome, Hallermann-Streiff syndrome, and Kenny syndrome [Aarksog and Harrison et al., 1994; Fanconi et al., 1986].

The development of diabetes mellitus, in combination with congenital hypoparathyroidism, has not been described in infancy to our knowledge. The commonest cause of insulinopenic diabetes mellitus in infancy is probably autoimmune-mediated beta cell destruction [Neufeld et al., 1980; Arslanian et al., 1985; Lendrum et al., 1975]. However, we found no evidence of autoimmune pancreatic involvement in our patient. Nonautoimmune insulinopenia has been reported in several syndromes, some signs of which overlap with those of our patient. A syndrome of diabetes mellitus, deafness, megaloblastic anemia, and ECG changes has been described in children as young as 19 months [Haworth, 1982; Rotig et al., 1992; Vianna and Carvalho, 1978]. Another syndrome, characterized by diabetes mellitus, mental retardation, deafness, ECG changes, alopecia, and hypogonadism, has been described in adolescents and adults from two Saudi families [Woodhouse and Sakati, 1983]. Although our patient has some phenotypic similarities to the individuals described in these reports, the multiple endocrine involvement during infancy and the progressive and fatal multisystem dysfunction distinguishes him from the patients previously described.

Hypoparathyroidism, diabetes mellitus, and primary hypothyroidism may occur as part of the multisystem involvement which characterizes disorders of energy production. The generation of metabolic energy is a complex, multi-enzymatic process, occurring primarily in the mitochondria. As such, mitochondrial diseases

may result in multisystem failure. In fact, multiple endocrinopathies are common in patients with mitochondrial diseases. Diabetes mellitus is the most frequently reported endocrine disease [Dunbar et al., 1993; Gerbitz et al., 1993; Goto et al., 1991; Johns et al., 1993; Johns et al., 1993; Kelley et al., 1982; Kishimoto et al., 1995; Luder and Barash 1994; Majander et al., 1991; Moares et al., 1989; Munnich et al., 1992; Newman et al., 1991; Pilz et al., 1991; Poulton et al., 1994; Remes et al., 1993; Rogers et al., 1969; Rotig et al., 1992; Superti-Furga et al., 1993; Suzuki, 1994; Zupanc et al., 1991] but hypoparathyroidism [Zupanc et al., 1991], growth hormone deficiency [Eviatar et al., 1990; Niaudet et al., 1994], and hypogonadism [Mosewitch et al., 1993; Newman, 1991] have also been described. Depending on the distribution and numbers of abnormal mitochondria, phenotypic manifestations of mitochondrial diseases may also include failure to thrive [Eviatar et al., 1990; Newman et al., 1991; Oldfors et al., 1990; Rogers et al., 1969; Rotig et al., 1993; Rotig et al., 1993; Simonz et al., 1992; Superti-Furga et al., 1993; Suzuki, 1994; Zupanc et al., 1991], encephalopathy [de Vriess et al., 1993; Gerbitz et al., 1990; Goto et al., 1991; Holt et al., 1990; Mosewitch et al., 1993; Zeviani et al., 1988; Zupanc et al., 1991], myopathy [de Vreiss et al., 1993; Dunbar et al., 1993; Eviatar et al., 1990; Goto et al., 1991; Holt et al., 1990; Moares et al., 1989; Mosewitch et al., 1993; Niaudet et al., 1994; Poulton et al., 1994; Tatuch et al., 1992; Zeviani et al., 1990; Zeviani et al., 1988; Zupanc et al., 1991], nephropathy [Luder and Barash, 1994; Majander et al., 1991; Nikoskelainen et al., 1987; Rotig et al., 1993; Superti-Furga 1993; Zupanc et al., 1991], and pigmentary retinopathy [Eviatar et al., 1990; Howell et al., 1991; Huoponen et al., 1991; Johns et al., 1993; Larsson et al., 1990; Moares et al., 1989; Newman et al., 1991; Nikoskelainen et al., 1987; Oldfors et al., 1990; Poulton et al., 1994; Shanske et al., 1990; Wallace et al., 1988; Zupanc et al., 1991]. Sensorineural deafness [Eviatar et al., 1990; Gerbitz et al., 1993; Goto et al., 1991; Kishimoto et al., 1995; Oldfors et al., 1990; Poulton et al., 1994; Remes et al., 1993; Rotig et al., 1993; Shanske et al., 1990; Zupanc et al., 1991], blindness [Howell et al., 1991; Huoponen et al., 1991; Johns et al., 1993; Newman et al., 1991; Nikoskelainen et al., 1987; Rotig et al., 1993], anemia [Larsson et al., 1990; Majander et al., 1991; Niaudet et al., 1994; Simonsz et al., 1991; Superti-Furga et al., 1993; Zupanc et al., 1991], lactic acidosis [Gerbitz et al., 1993; Goto et al., 1991; Holt et al., 1990; Luder and Barash, 1994; Remes et al., 1993; Rotig et al., 1992; Superti-Furga et al., 1993; Suzuki, 1994; Tatuch et al., 1992; Zupanc et al., 1991], cardiac dysfunction [Gerbitz et al., 1990; Gerbitz et al., 1993; Larsson et al., 1990; Oldfors et al., 1990; Poulton et al., 1994; Shanske et al., 1990; Zeviani et al., 1990], exocrine pancreatic insufficiency [Majander et al., 1991; Niaudet et al., 1994; Simonsz et al., 1992; Superti-Furga et al., 1993], and cerebellar dysfunction [Larsson et al., 1990; Rotig et al., 1992; Zeviani et al., 1990] have also been reported.

The constellation of findings, and their inexorable progression, in our patient is strongly suggestive of a mitochondrial cytopathy. If so, our patient is the youngest reported patient with such widespread endocrine failure with onset in the neonatal period. Multiple endocrinopathies have been described in older children and adults with known mitochondrial disease [Eviatar et al., 1990; Zupanc et al., 1991]. However, standard textbooks of pediatric endocrinology have, thus far, not included mitochondrial disorders in the etiology of endocrine diseases [Aarskog and Harrison, 1994; Mimouni and Tsang, 1990]. In particular, hypoparathyroidism presenting in the neonatal period, or hypothyroidism and diabetes mellitus manifesting in early infancy [Aarskog and Harrison, 1994; Mimouni and Tsang, 1990], have not been noted.

We have searched for a mitochondrial basis for our patient's problems. However, we have not demonstrated any large deletion or duplication of mitochondrial DNA in skeletal muscle or peripheral leukocytes. Furthermore, we have not found mutations at basepairs 3243 [Gerbitz et al., 1993; Kishimoto et al., 1995], 3271 [Goto et al., 1991], and 8993 [de Vriess et al., 1993; Holt et al., 1990] which have been previously reported in patients with some mitochondrial diseases. Since mitochondrial proteins are coded by many nuclear as well as mitochondrial genes, it is conceivable that defects in nuclear genes could also result in decreased energy production. Thus, defects in either of these genomes can result in decreased energy production at the cellular level, resulting in widespread manifestations similar to those detailed in our patient. To date, our attention has focused on the mitochondrial genome.

In summary, we have described an infant with relentlessly progressive multisystem dysfunction with onset of polyendocrinopathy in the immediate neonatal period. A diagnosis has not yet been established. It is possible that MP has a more severe and extensive form of the syndrome described in Saudi, Kuwaiti, and Asian children with hypoparathyroidism [Richardson and Kirk, 1990; Sanjad et al., 1991; Shaw et al., 1991]. On the other hand, his clinical findings are remarkably similar to those found in patients with mitochondrial diseases. In fact, we speculate that the children described in the Middle Eastern and Asian kindreds may have mitochondrial abnormalities. In any case, we think that our patient has an, as yet, unrecognized syndrome. We suggest that disorders of energy production should be considered in all neonates and children with endocrine failure.

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